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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,674	11/13/2003	Ken Y. Lin	STAN-276	9855
24353	7590	09/24/2007	EXAMINER	
BOZICEVIC, FIELD & FRANCIS LLP 1900 UNIVERSITY AVENUE SUITE 200 EAST PALO ALTO, CA 94303			VENCI, DAVID J	
		ART UNIT	PAPER NUMBER	
		1641		
		MAIL DATE	DELIVERY MODE	
		09/24/2007	PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/713,674	LIN ET AL.
	Examiner	Art Unit
	David J. Venci	1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on June 1, 2007.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-9, 15 and 17-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-9, 15 and 17-19 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date: _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Examiner acknowledges receipt of Notice of Appeal and Appeal Brief, filed April 17, 2007, and June 1, 2007, respectively. Herein, Examiner raises new grounds for rejection in view of the teachings of Ogawa *et al.*, 252 Arch. BIOCHEM. BIOPHYS. 526 (1987), and Cooper & Meister, 253 J. BIOL. CHEM. 5407 (1978). The teachings of Ogawa *et al.* and Cooper & Meister raise new issues under 35 USC § 112, first paragraph and 35 USC § 102.

The finality of the Office Action dated October 18, 2006, is withdrawn.

Claims 1-9, 15 and 17-19 are pending.

Claim Rejections - 35 USC § 112 – first paragraph

Claims 1-9, 15 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.¹

Independent claim 1 recites a method of detecting asymmetric dimethylarginine (ADMA) in a sample comprising ADMA and at least one of symmetric dimethylarginine (SDMA) and arginine. Claim 1 requires contacting a sample with an α -dicarbonyl compound, then detecting ADMA.

¹ According to the decision in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of

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The specification does not enable any method approximating the broadly claimed two-step method. Instead, the specification describes a method requiring:

1. solid phase extraction of a biological sample;²
2. reacting the product of 1) with o-phthaldialdehyde and an α -dicarbonyl compound;³
3. solid phase extraction of the product of 2) and ADMA detection;⁴ AND

Applicants' specification provides minimal direction and no working examples successfully performing the claimed two-step. Although the specification lists steps 1-3, *supra*, the specification does not clearly describe procedural details for o-phthaldialdehyde derivatization, such as reaction duration, whether/how the reaction is terminated, whether/how reaction products are isolated from the reaction mixture, or what reaction products are formed. More importantly, the specification does not clearly describe the procedural details for α -dicarbonyl derivatization, such as whether/how o-phthaldialdehyde derivatives can react with α -dicarbonyl compound, or how to detect ADMA in the product of a reaction between a sample with o-phthaldialdehyde and an α -dicarbonyl compound.

The state of the prior art appears to recognize a high degree of unpredictability in the field of arginine chemical derivatization. Specifically:

1. α -dicarbonyl compounds bind to cysteine, lysine and anything hydrophobic. Such non-specific, indiscriminate, unpredictable α -dicarbonyl activity necessarily affects α -dicarbonyl activity with respect to SDMA and arginine, as contemplated in claim 1, step a). See e.g., Baburaj *et al.*, 1199 BIOCHIM. BIOPHYS. ACTA 253 (1994), describing two α -dicarbonyl compounds (see Title,

direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

² See e.g., Substitute Specification paragraphs [0051] and [0052].

³ See e.g., Substitute Specification paragraph [0053].

⁴ See e.g., Substitute Specification paragraphs [0054] to [0071].

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"HOCGO" and "DMACGO") capable of reaction with cysteine, lysine and hydrophobic surfaces (see p. 262, right column, Section 4.2).

2. α -dicarbonyl compounds react with arginines to produce multiple arginine derivatives. These arginine derivatives necessarily affect α -dicarbonyl activity with respect to SDMA and/or arginine, as contemplated in claim 1, step a). See e.g., Schwarzenbolz *et al.*, 205 Z. LEBENSM. UNTERS FORSCH. A 121 (1997), noting that under certain reaction conditions, the α -dicarbonyl compound, glyoxal, produces two arginine derivatives (see Fig. 3). See also, Sopio & Lederer, 201 Z. LEBENSM. UNTERS FORSCH. A 381 (1995), teaching that, under certain experimental conditions, the α -dicarbonyl compound, deoxyosones, results in two tautomeric products (see Fig. 6).
3. α -dicarbonyl compounds react with ADMA. Such ADMA derivatives necessarily affect α -dicarbonyl activity with respect to SDMA and/or arginine, as contemplated in claim 1, step a). More importantly, such a reaction necessarily eliminates ADMA from the ADMA assay. See e.g., Cooper & Meister, 253 J. BIOL. CHEM. 5407 (1978), showing that α -dicarbonyl compounds can react with arginyl ϵ -nitrogen, and that arginyl η -nitrogens are not required for guanidino reactivity with α -dicarbonyl compounds (see Fig. 1).

Given the aforementioned deficiencies in Applicants' disclosure, Examiner posits that the quantity of experimentation needed to perform the claimed two-step method of detecting ADMA is undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Ogawa *et al.*, 252 Arch. BIOCHEM. BIOPHYS. 526 (1987) (annotations added).

Ogawa *et al.* describe a method of detecting asymmetric dimethylarginine (ADMA) comprising:

- a) contacting a sample with an α -dicarbonyl compound (see p. 529, paragraph bridging left and right columns, last sentence, "radioactive metabolites obtained from Peaks b[...] confirmed by cochromatography") (paraphrasing mine), wherein said sample comprises ADMA, SDMA and arginine (see Fig. 2); and
- b) detecting ADMA (see Figs. 1 and 2, Tables I-III).

Examiner posits that Ogawa *et al.* describe α -dicarbonyl compounds (*i.e.*, α -ketoacid analogs) that inherently modify guanidino nitrogens, and would be so recognized by persons of ordinary skill. See e.g., Cooper & Meister, 253 J. BIOL. CHEM. 5407 (1978), showing that α -dicarbonyl compounds can react with arginyl ϵ -nitrogen, and that arginyl η -nitrogens are not required for guanidino reactivity with α -dicarbonyl compounds (see Fig. 1).

Response to Arguments

Claim Rejections - 35 USC § 112 – first paragraph

In prior Office Action, claims 1-9, 15 and 17-19 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

In response, Applicants argue five main points:

1. The specification provides ample guidance.
 - a. The specification provides ample description of how to modify the guanidino nitrogens of SDMA and arginine.
 - b. The specification provides ample description of method for detecting ADMA.
 - c. The specification contemplates use of any of a variety of α -dicarbonyl compounds, and provides a number of such compounds.
2. The claims are not unduly broad.
3. No undue experimentation would be required to practice the claimed invention.
4. The skill level of those in the relevant field was high as of November 15, 2002.
5. The cited art does not support a conclusion of lack of enablement of the instant claims.

Applicants' arguments have been carefully considered but are not persuasive.

With respect to 1), the specification does not provide guidance for *the claimed method*. Examiner respectfully asserts that Applicants' invention is not a method for modifying guanidino nitrogens of SDMA and arginine. Nor is Applicants' invention a method of contemplating what α -dicarbonyl compounds might be useful. Rather, Applicants claim a method requiring contacting a sample with an α -dicarbonyl compound AND then detecting ADMA. However, the specification does not provide guidance for this

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claimed method. Instead, the specification describes a method requiring extracting a sample,⁵ reacting the extracted sample with *o*-phthaldialdehyde and an α -dicarbonyl compound,⁶ and extracting and/or detecting ADMA in the reacted sample.⁷

With respect to 2), the specification provides no working examples successfully performing the claimed two-step method, much less a particular α -dicarbonyl compound successfully used in the claimed two-step method.

With respect to 3), Applicants claim a method requiring contacting a sample with an α -dicarbonyl compound AND then detecting ADMA. The specification does not provide guidance for this *claimed* two-step method. Instead, the specification describes a method requiring extracting a sample,⁸ reacting the extracted sample with *o*-phthaldialdehyde AND an α -dicarbonyl compound,⁹ and extracting and/or detecting ADMA in the reacted sample.¹⁰

The description of the *o*-phthaldialdehyde/ α -dicarbonyl derivatization procedure in the specification provides no guidance as to how to practice the *claimed* invention because the description of the derivatization procedure in the specification is incomplete. The description of the derivatization procedure in the specification does not specify reaction duration, whether/how the reaction is terminated, whether/how reaction products are isolated from the reaction mixture, what reaction products are formed, whether/how *o*-phthaldialdehyde derivatives can react with α -dicarbonyl compound, or how to detect ADMA in the product of a reaction between a sample with *o*-phthaldialdehyde and an α -dicarbonyl compound. The specification does not provide a complete description of the specification method, much less the claimed two-step method.

⁵ See *supra*, note 2 and citing text.

⁶ See *supra*, note 3 and citing text.

⁷ See *supra*, note 4 and citing text.

⁸ See *supra*, note 2 and citing text.

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Thus, given the specification's incomplete description of the claimed method, and the inevitably resulting questions which skilled artisans must answer, Examiner posits that the quantity of experimentation needed to perform the claimed two-step method of detecting ADMA is undue.

With respect to 4), according to M.P.E.P. § 716.01(c), Applicants must factually support any objective evidence with an appropriate affidavit or declaration to be of probative value. Such objective evidence should be commensurate in scope to Applicants' claimed two-step method.

With respect to 5), the cited prior art provide ample evidence of the non-specific, indiscriminate, unpredictable behavior of α -dicarbonyl compounds and α -dicarbonyl activity with respect to SDMA, arginine and ADMA. Furthermore, Cooper & Meister, 253 J. BIOL. CHEM. 5407 (1978), cited herein, provide evidence that α -dicarbonyl compounds can react with arginyl ε -nitrogen, and that arginyl η -nitrogens, regardless of their degree of methylation, are not required for guanidino reactivity with α -dicarbonyl compounds (see Fig. 1). Such a reality further confounds the claimed ADMA assay.

Applicants must provide basis for the mantra that "all that is required is that the α -dicarbonyl compound modify any SDMA and any arginine that may be present in the sample".

Claim Rejections - 35 USC § 112 – second paragraph

In prior Office Action, claim 1 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite because the passive voice phrase "said modified SDMA and said modified arginine are distinguishable" was considered indefinite. The identity of object(s) and/or step(s), if any, required for performing distinguishing is not clear. This rejection has been principally withdrawn.

⁹ See *supra*, note 3 and citing text.

¹⁰ See *supra*, note 4 and citing text.

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Conclusion

No claims are allowable at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is 571-272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Assistant Examiner
Art Unit 1641

djv

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